Chapter 1

General introduction

1.1 Image-guided radiotherapy

Radiotherapy is a treatment modality for cancer using high-energy ionizing radiation. The deposition of ionizing radiation causes damage to the cells in the treated area. This damage can result in cell dead (Rubin, 2001). The most common form of radiotherapy is external beam irradiation with high-energy photons. Radiotherapy aims to deliver high doses to the area containing malignant cells, while sparing the normal tissue adjacent to this area. Models based on simple biophysical assumptions have been developed to predict the tumor control probability (TCP) (Brenner, 1993; Webb, 1993). Depending on the radiosensitivity and the volume of clonogenic cells with a certain cell density, the TCP can be predicted for an inhomogeneous dose distribution. These models indicate that, for the same biological effect, higher doses are needed when more clonogenic cells are present in the target volume and when the tumor cells are relatively insensitive to radiation. Ideally, when tumor specific data are available, this should result in dose painting, i.e. creating a heterogeneous dose distribution within the target based on tumor characteristics, such as radiosensitivity, clonogenic cell density and tumor hypoxia (Ling et al., 2000).

In order to perform dose painting, radiotherapy should be image guided. Images should provide anatomical and biological data. The advent of computed tomography (CT) and magnetic resonance imaging (MRI) made it possible to visualize the human anatomy. Using this anatomical information three-dimensional conformal radiotherapy (3D-CRT) (Webb, 1997) could be developed. 3D-CRT is used to avoid as much as possible irradiation of the surrounding tissue and at the same time deliver the prescribed dose to the target. Sharper dose gradients and a better homogeneity of the dose within the target can be achieved when intensity-modulated radiotherapy (IMRT; Webb (2001)) is applied, which is an advanced form of 3D-CRT. Instead of using a uniform beam intensity, IMRT uses non-uniform beam
intensities to provide more degrees of freedom for dose shaping. IMRT can also be used for dose painting within the target volume. Positron emission tomography (PET), nuclear magnetic resonance imaging (MRI) and spectroscopy (MRS) are beginning to provide physical and functional information about the tumor and its surroundings (Ling et al., 2000). The use of these imaging techniques for radiotherapy is, however, still under development, and full dose painting is not yet possible. For conventional radiotherapy the prescribed tumor dose is usually limited by the dose to the surrounding critical organs. The first attempt to dose painting using IMRT is, therefore, to escalate the dose within the gross tumor volume (GTV) (Nederveen et al., 2001b; Mohan et al., 2000; Zelefsky et al., 2000).

Due to the sharp dose gradient between critical organs and the tumor, special attention should be paid to the localization of the tumor when using IMRT. The position of the tumor during the imaging process needed for the IMRT planning, should be the same as during the actual treatment, to assure that the dose is delivered to the right spot. Misalignment of the patient, or organ motion, may result in underdosage to the tumor sites and overdosage to critical organs. It is therefore important to determine and manage geometrical uncertainties (Langen and Jones, 2001; Jaffray et al., 1999) for IMRT treatments. Ideally, the position of the target should be visualized during the treatment.

1.2 IMRT delivery

There are several methods to delivered intensity-modulated beams. The main clinically available methods use compensator filters, multi-leaf collimators (MLCs), or tomotherapy (Webb, 1997; IMRT Collaborative Working Group, 2001). Like at many other institutes, most linear accelerators at our department are nowadays equipped with a MLC. The MLC consists of a set of thin blades, which can be individually positioned, and therefore create irregularly shaped beams. There are two approaches of IMRT delivery using MLC: the dynamic and segmental MLC approach. Using a dynamic MLC (DMLC) technique, each pair of MLC leaves moves during irradiation. By changing the setting of the leaf pair opening and the speed of the leaves, it is possible to create intensity-modulated beams. The segmental approach uses a series of multiple segmental fields (Fig. 1.1). The method is also called step-and-shoot, because the beam is off when the leaves move to the next position. By adding the individual shaped segmental fields, an intensity-modulated beam is created. To obtain these segments, the optimized intensity profile is divided in a discrete number of intensity levels.

The advantage of the DMLC technique is that the delivered intensity profile closely matches the intended profile. When using segmental IMRT the intended profile is approximated by a discrete number of segments. The conversion of the optimized
1.3. Geometric uncertainties in radiotherapy

The location of the tumor is not exactly at the same position during the course of the radiotherapy, due to geometric uncertainties, such as patient positioning errors, patient movement and organ motion. Differences between the actual position and the position during the planning, lead to misalignment between the treatment fields and the tumor. To avoid possible reduction in TCP, the field size has to be extended. In other words, an extra margin is added to the target volume, resulting in a planning target volume (section 1.4.2), to ensure the that target is irradiated with the prescribed dose (Fig. 1.2). This leads to an extra dose to the normal tissue adjacent to the target, which can result in an increased normal tissue complication probability (NTCP). The prescribed dose to the tumor is consequently often limited by the dose to the surrounding normal tissue.

The geometric uncertainties can result in a change of the position of the target relative to other fractions (interfraction motion), and within a single fraction (intrafraction motion). Intrafraction motion can, for example, occur due to positioning errors or changes in patient anatomy such as weight loss. Organ motion can also result in interfraction motions. In the pelvic region this is often caused by the filling of organs such as the bladder and intestinals (Langen and Jones, 2001; Jaffray et al., 1999). Intrafraction motion is caused by periodic motions, such as breathing and cardiac motion, or due to instant motions, such as gas motion, clenching of muscles and swallowing (Langen and Jones, 2001; Jaffray et al., 1999).

All geometric uncertainties contribute to an error in the alignment between the target and the treatment fields. This error can be separated in systematic and random errors (Van Herk et al., 2000). Systematic errors are deviations between the
average target positioning during the treatment and the planned target position. Since the total dose of a radiotherapy treatment is the sum over all fractions, the systematic error causes a shift in the total dose distribution. Random errors are deviations between each fraction and occur day to day. These result in a blurring of the total dose distribution.

1.4 Management of geometric uncertainties

1.4.1 Position verification using and EPID

In order to minimize geometric uncertainties, position verification is needed. After verification of the position of the target, the position can be corrected using a correction protocol (Bel et al., 1993; De Boer et al., 2001). Most correction protocols aim at minimizing the systematic errors and are off-line. Using an off-line correction protocol, the position of the target is verified after a single treatment session. The next session the position can be corrected. The ultimate goal of position verification is, to ensure, that the target is located at the same position relative to the treatment fields during all radiotherapy fractions. To achieve that goal online position verification and correction should be applied. Both the random and the systematic errors can than be removed.

Many institutes use portal imaging to measure set-up errors by applying a megavoltage film or an electronic portal-imaging device (EPID). Using these portal images, the bony structures can be used as internal markers (Fig. 1.3), of which the location can be verified with respect to their location in the reference position (Hurkmans et al., 2001b). The reference position is thereby the position during the imaging process used for the radiotherapy planning. The use of the bony structures for position verification of the target is indirect, the location of the target should
1.4. Management of geometric uncertainties

Figure 1.3: An example of a reference image (a) and a portal image (b) taken during the treatment for head-and-neck cancer. Beside the bony structures two markers are visible. The location of markers is indicated by two arrows.

Therefore not change relative to the bony structures. For many head-and-neck cancers the targets do not move relative to the bony structure, while for cancers in the pelvic region target volumes may show motions relative to the bony structures.

Instead of the use of bony structures, radiopaque markers can be used for position verification (Nederveen et al., 2001a; Shirato et al., 2000; Litzenberg et al., 2002). These markers are usually made of gold. Due to their high electron density, they can be visualized in a portal image (Fig. 1.3). The location of these markers should be fixed relative to the target. The best place to put the markers would be the target itself, since the location of the markers would than be the best representation of the target. This is, however, not possible for each target. Some targets can deform during the radiotherapy course; markers within such targets are not reliable for position verification. Although the use of implanted markers is invasive, it has several advantages. When the target can move relative to the bony structures, the marker, in case its location is fixed to the target, better represents the target location. In that case markers can be used to remove the systematic errors, while using bony structures this is not possible. Another benefit of the use of markers is that the determination is straightforward in images and a small number of monitor units is sufficient to obtain a suitable portal image. This facilitates automatically detection of the markers within the portal images. Marker-based position verification can therefore also be used for measuring intrafraction motions. Furthermore, markers can be detected in small fields as used for IMRT treatments, while the use of bony structures is difficult when only small fields are used.
1.4.2 PTV-CTV margin

The clinical target volume (CTV) should be treated adequately in order to achieve the aim of radical therapy (ICRU Report No. 62, 1999). The CTV is a tissue volume that contains the gross tumor volume (GTV) and/or subclinical malignant disease that must be eliminated (ICRU Report No. 62, 1999). Due to the geometric uncertainties in the location of the CTV relative to the treatment field, a margin should be added to the CTV (Fig. 1.2). If no margins are added to the CTV some tissue may, for part of the treatment move out of the beam. The resulting volume is the planning target volume (PTV). This is a geometrical concept used for treatment planning, and it is defined to select appropriate beam sizes and beam arrangements, to ensure that the prescribed dose is actually delivered to the CTV (ICRU Report No. 62, 1999).

Both the random ($\sigma$) and systematic ($\Sigma$) positioning errors contribute to the margin between the CTV and the PTV. For a margin that ensures 95% minimum dose for 90% of the patients the following recipe was derived by Van Herk et al. (2000) when perfect conformation is assumed in 3D and 2D respectively:

$$Margin(3D) = 2.5\Sigma + 0.7\sigma$$  \hspace{1cm} (1.1)
$$Margin(2D) = 2.15\Sigma + 0.7\sigma$$  \hspace{1cm} (1.2)

A similar recipe was derived by Stroom et al. (1999) (equation 1.3). The criterion to derive the recipe was that on average more than 99% of the CTV should at least get 95% of the dose.

$$Margin = 2\Sigma + 0.7\sigma$$  \hspace{1cm} (1.3)

The differences between the recipes might be due to the fact that different criterions were used. Both recipes demonstrate the large contribution of the systematic error to the margin. Using position verification to minimize the geometric uncertainties and thus reduce the margin, the main effort should be to reduce the systematic error. This can be achieved using marker-based position verification. The benefit of the use of markers is that it can be used as a direct verification of the target, since these can be placed inside the target (Nederveen et al., 2001a). Systematic errors can therefore be removed for targets loosely attached to the bony anatomy.

1.5 Clinical applications of IMRT

1.5.1 IMRT for breast cancer

Many patients have been successfully treated with breast conserving radiotherapy (Fisher et al., 1989; van Dongen et al., 1992; Morris et al., 1997). The gross tumor
1.5. Clinical applications of IMRT

is thereby surgical removed and the entire breast is treated with radiotherapy in order to control the subclinical disease. The aim for breast conserving radiotherapy is to deliver a homogeneous dose of 50 Gy (2Gy/fraction; 5 times weekly) to the breast, which can be followed by a small boost dose of 14-20 Gy (2Gy/fraction; 5 times weekly) to the tumor bed (Bartelink et al., 2001). The advent of CT made it possible to visualize the anatomy of the breast and to calculate and analyze the three-dimensional dose distribution. The dose homogeneity of the breast has been studied by several groups (Buchholz et al., 1997; Carruthers et al., 1999; Cheng et al., 1994; Neal et al., 1995; Solin et al., 1991). Using conventional techniques, such as wedged fields, it is not always possible to achieve a homogeneous dose distribution due to the complex geometry of the breast. The inhomogeneities typically occur at the entry points, the most caudal en cranial part of the treated volume and the nipple. An inhomogeneous dose is believed to be a contributing factor to the cosmetic result after radiotherapy (Moody et al., 1994), because poor cosmesis occurs more often in patients with large breasts (Gray et al., 1991; Moody et al., 1994; Vrielings et al., 2000) and the dose inhomogeneity of these patients is larger compared to patients with smaller breasts (Buchholz et al., 1997; Cheng et al., 1994; Neal et al., 1995). The dose homogeneity can be improved by beam intensity modulation. Beside the ability to improve the dose homogeneity, IMRT might be used to decrease the dose to the lung and the heart. This is important since side effects due to irradiation of the breast, such as ischemic heart disease (Gyenes et al., 1998) and radiation pneumonitis (Kwa et al., 1998), may occur.

Beside setup errors, organ motion due to breathing will contribute to the margin taken for geometrical uncertainties. The intra- and interfraction reproducibility of tangential breast irradiation has been determined using an EPID (Fein et al., 1996; Lirette et al., 1995; van Tienhoven et al., 1991). One of the parameters studied is the central lung distance (CLD), which is the distance from the posterior field margin to the inner chest wall along the horizontal axis of the field. For normal respiratory function, the standard deviation of the intrafraction motion is reported 1-2 mm. The standard deviation of the reported random errors is higher, 2 - 4.4 mm, and the variations in the systematic error are 3-4 mm.

1.5.2 IMRT for Head & Neck cancer

Oropharyngeal cancer

For the treatment of cancers in the head-and-neck region different treatment strategies are used, such as surgery, radiotherapy, chemotherapy or combinations of these modalities. Almost all early oropharyngeal tumors (T1 and T2) are treated with radiation therapy alone. The aim at our department is to deliver a dose of 46-50 Gy (2Gy/fraction; 5 times weekly) to the microscopic disease and 70 Gy (2Gy/fraction; 5 times weekly) to the macroscopic disease (primary tumor and positive lymph nodes). The dose to the target is often limited by the maximum dose
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to critical organs adjacent to the targets, such as the spinal cord and brain (Emami et al., 1991). Another severe complication is xerostomia, caused by irradiation of the salivary glands (Chao et al., 2001; Eisbruch et al., 1999; Roesink et al., 2001). The use of CT made it possible to delineate all target volumes and organs at risk. A simple form of dose painting can be created, when different dose levels are assigned to the individual volumes. The primary tumor and the lymph nodes will thereby receive a different dose, while at the same time the dose to the organs at risk is minimized. In order to develop such a technique, IMRT can be used. With IMRT the different dose levels to the primary tumor and the lymph nodes can be delivered simultaneously. However, other fractionation strategies should than be developed compared to conventionally used (Mohan et al., 2000). Using IMRT it is even possible to deliver a higher dose than conventionally given, in other words to escalate the dose, while sparing surrounding normal tissues. There are several studies indicating that dose escalation might be useful. For oropharyngeal cancer local-regional recurrences after radiotherapy occur most frequently at the site of the original tumor (Pigott et al., 1995). It has also been reported that when using conformal or segmental IMRT most recurrences occurred within the areas judged to be of high risk at the time of the radiotherapy planning (Dawson et al., 2000a). Furthermore it has been shown that a higher total dose and reduction of the treatment time could improve the local control for oropharyngeal tumors (Maciejewski et al., 1989; Withers et al., 1995b).

In order to deliver a high conformal dose distribution and prevent high doses to critical structures, accurate patient positioning is essential. Usually patients treated for head-and-neck cancer are immobilized using a thermoplastic mask. Position verification is performed with a megavoltage film or EPID, where the location of the bony structures within the treatment fields is determined. The random and the systematic error amount to approximately 2 mm (1 standard deviation) (Hurkmans et al., 2001b). Intrafraction displacements have not yet been quantified for patients with head-and-neck cancer.

Preservation of the salivary glands

During radiotherapy of head-and-neck cancers, the parotid gland is often exposed to radiation, which can cause severe reduction of salivary flow and change in salivary composition. This may result in xerostomia, difficulties in mastication and speech, changes of taste, increased risk of carries and oral infections, chronic esophagitis and altered nutrition (Hamlet et al., 1997; Mandel, 1987; Vissink et al., 1988; Wright, 1987). These severe side effects have a negative impact on the quality of life of the patient (De Graeff et al., 1999; Huguenin et al., 1999). Although with IMRT highly conformal plans can be achieved, there is still a significant dose to the parotid gland because the lymph nodes are located adjacent to the parotid glands. The PTV of the lymph nodes will therefore overlap with the parotid glands. When
no reduction of the TCP is allowed, this part of the parotid glands should receive
the prescribed dose.

1.6 Outline of this thesis

In chapter 2 the development of a segmental IMRT technique using 3D geometrical
information for tangential breast irradiation is presented. The IMRT technique is
applied to achieve a homogeneous dose distribution through the entire breast. The
shape of the individual segments was obtained from an equivalent path length map
of the irradiated volume.

In chapter 3 segmental IMRT is applied for the treatment of oropharyngeal cancer,
which is a more complex case than the breast. Different dose levels are delivered
to the primary tumor, the CTV of the primary tumor and the CTV of the lymph
nodes, while the dose to surrounding organs at risk is minimized. This can be
considered a simple form of dose painting. The relation between the quality of the
treatment and the number of beams in combination with the number of segments is
investigated. This information will be used for developing an efficient and reliable
segmental IMRT technique.

Chapter 4 deals with the dose to the parotid gland. Using the segmental IMRT
technique presented in the previous chapter, the dose to the parotid gland is re-
duced without compromising the dose to the targets. Due to the margin taken for
geometrical uncertainties, the PTVs will partially overlap with the parotid glands.
This causes a high dose area in the parotid glands. The effect of reduction of
positioning margins is presented in this chapter.

In chapter 5 the feasibility of the use of implanted gold markers for position ver-
ification in the head-and-neck region is investigated using an EPID. Accurate
position verification is needed to deliver the dose at the right spot, particularly
for highly conformal plans created with IMRT. Markers were implanted in ten
patients and the toxicity and the reliability of marker-based position verification
was studied.

In chapter 6 intrafraction motions in the larynx are studied. Although most struc-
tures in the head-and-neck are relatively immobile, the larynx is a rather mo-
bile organ. Due to the high image quality of the EPID, the displacements of the
anatomical structures could be determined for 10 patients during radiotherapy.

A general discussion is presented in chapter 7. Imaging in radiotherapy, IMRT for
breast cancer and IMRT for oropharyngeal cancer will be discussed separately.